JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 10, Number 1, 1991
Mary Ann Liebert, Inc., Publishers

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Final Report on the Safety Assessment of *p*-Methylaminophenol Sulfate

p-Methylaminophenol Sulfate is a substituted phenol used as a dye and a photographic developer. In skin absorption studies of radioactive p-aminophenol, as much as 11% of the radioactivity was found in the excreta, viscera, and skin of rats.

In subchronic and chronic dermal toxicity studies of hair dyes containing p-Methylaminophenol Sulfate, among other active ingredients, no toxicologically significant differences were observed between the test and control animals. In an ocular irritation study, this ingredient was considered practically nonirritating to the rabbit eye and only slightly irritating to the skin and was not a sensitizer.

No significant embryotoxic or teratogenic effects were found when hair dyes containing p-Methylaminophenol Sulfate were administered to rats.

***p*-Methylaminophenol was not mutagenic in the Ames assay nor in the mouse micronucleus assay and in the Chinese hamster ovary chromosome aberration test. No statistically significant incidences of neoplasms, dermal and other, were found in mice after 21 and 23 months of weekly dermal exposure to hair dyes containing p-Methylaminophenol Sulfate.**

When p-Methylaminophenol Sulfate was tested in 200 eczema patients without known previous contact with the chemical, 1 patient had a positive reaction.

On the basis of the available data presented in this report, it is concluded that p-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

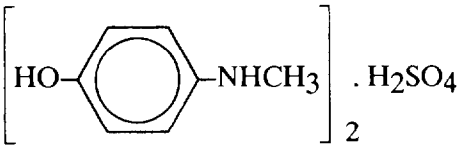
INTRODUCTION

The following report is a literature review on the chemistry, use, and toxicology of the oxidative hair dye ingredient *p*-Methylaminophenol Sulfate. *p*-Methylaminophenol Sulfate is a substituted *p*-aminophenol, and thus data found in the reports on the aminophenols, as well as on other oxidative hair dye ingredients, such as the phenylenediamines and resorcinols, are useful in the evaluation of the safety of *p*-Methylaminophenol Sulfate. These reports, previously prepared by the Cosmetic Ingredient Review and referenced below, are only summarized here.

CHEMISTRY

Definition and Structure

p-Methylaminophenol Sulfate is a substituted phenol used as a dye and a photographic developer. *p*-Methylaminophenol Sulfate (CAS No. 55-55-0) is also known as 4-Methylaminophenol Sulfate,[1] N-Methyl-*para*-aminophenol Sulfate,[2] Monomethyl-*p*-aminophenol Sulfate, *p*-Hydroxymethylaniline Sulfate, and commercially as Metol, Pictol, Rhodol, and various other names.[3] It conforms to the following structure:



p-Methylaminophenol Sulfate

PROPERTIES

p-Methylaminophenol Sulfate occurs as colorless needles[2] or other crystalline products.[3] On exposure to air, *p*-Methylaminophenol Sulfate becomes discolored.[2,3] It has a molecular weight of 344.39 and a melting range between 250°C and 260°C.[4] Decomposition of *p*-Methylaminophenol Sulfate occurs upon melting.[3] It is soluble in water,[2,3,4] slightly soluble[3] to soluble[2,4] in alcohol, and insoluble in ether.[2,3]

Method of Manufacture

p-Methylaminophenol Sulfate is manufactured by the methylation of *p*-aminophenol and the subsequent neutralization with sulfuric acid.[2]

Analytical Methods

Infrared, ultraviolet, and nuclear magnetic resonance spectra have been published for *p*-Methylaminophenol Sulfate. The UV spectrum had peaks at 271 and 220 nm, with water as the solvent.[5] A UV spectrum also has been performed on *p*-Methylaminophenol at a concentration of 0.02 g/l in distilled water. The chemical absorbed at 219, 270, and 277 nm.[6] The compound may be determined by thin layer chromatography, using a method that depends on color rather than R_F values as a more reliable method for distinguishing among *o*-, *m*-, and *p*-isomers.[7] In addition, it may be analyzed by either visual or potentiometric titration with N-bromosuccinamide using the following indicators: butaperazine dimaleate, trifluoperazine dihydrochloride, or promethazine hydrochloride.[8]

Chemical Reactions

p-Methylaminophenol Sulfate is used as a primary intermediate in oxidative or permanent hair dyes.[9] The primary intermediate undergoes a reaction with hydrogen

peroxide (the oxidant) to produce the corresponding imine, which then reacts with a coupler to form an indophenol dye.[10] As an intermediate in combination with other intermediates, *p*-Methylaminophenol Sulfate is capable of producing browns, reds, gold blonds, blues, and grays.[9] More detailed accounts of the reactions of aminophenols and of oxidative hair coloring chemistry have been published previously.[11–14]

USE

Noncosmetic Use

p-Methylaminophenol Sulfate is used in spectrophotometric analyses of such compounds as dapsone,[15] isoniazid,[16] riboflavin,[17] and antibiotics[18] and in the colorimetric analyses of thiamine hydrochloride[19] and penicillins G and V.[16] It also is listed in various patents for pharmaceuticals as a treatment for neoplastic disease.[20,21] *p*-Methylaminophenol Sulfate also is used in film developing.[22]

Cosmetic Use

p-Methylaminophenol Sulfate is used as an intermediate in hair dyes/colors, which usually bear warning labels. According to information voluntarily supplied to the Food and Drug Administration,[23] *p*-Methylaminophenol Sulfate is used in a total of 49 hair dyes (Table 1). Its concentration of use ranges from ≤0.1% (31 products) to 0.1–1% (17 products). One product is listed at >5–10%; this is a powder concentrate that is to be diluted before use.

The FDA cosmetic product formulation computer printout[23] is compiled through voluntary filing of such data in accordance with Title 21 Part 720.4 of the Code of Federal Regulations.[24] Ingredients are listed in present concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product. The actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

The oxidative or permanent hair dyes containing *p*-Methylaminophenol Sulfate, as "coal tar" hair dye products,[11] are exempt from the principal adulteration provision and from the color additive provision in Sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation.[25] In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Patch test instructions call for a 24-h patch on the skin of the user with the intermediates and hydrogen peroxide mixed in the same manner as in use. This test is to be performed prior to each and every application of the hair dye.[26]

Reports containing a more in-depth review of the labeling requirements for "coal tar" hair dyes have been published. Hair dyes containing *p*-Methylaminophenol Sulfate may come into contact with the hair, skin, eyes, and nails, and may be applied every few weeks, or in the case of hairdressers, exposure may be several times daily.[11,12]

GENERAL BIOLOGY

Biochemical Effects

In a study of the effects of various chemicals on the depolarizing or hyperpolarizing effects of acetylcholine on the giant neurons of *Lymnea stagnalis*, *p*-Methylaminophenol Sulfate was inhibitory to the depolarizing action of acetylcholine in 92% of the giant neuron D cells tested. *p*-Methylaminophenol Sulfate did not enhance the action of acetylcholine in any test.[27]

The effects of aminophenols on hemoglobin and methemoglobin in the blood of various species were studied *in vivo* and *in vitro*.[28] In ox erythrocytes in Krebs-Ringer phosphate solution, *p*-Methylaminophenol Sulfate reacted with hemoglobin to form methemoglobin at a much faster rate (40×10^{-5} equiv/L/min) than did *p*-aminophenol. The reaction in dog erythrocytes was considerably faster than that in ox erythrocytes, with all of the *p*-Methylaminophenol Sulfate having disappeared from the solution within 10 min and with the methemoglobin concentration reaching its peak at 5 min. In the erythrocytes of both humans and rabbits, the rate of methemoglobin formation was a little faster than that of ox erythrocytes. When the *p*-Methylaminophenol Sulfate was added to a cell suspension already containing a high concentration of methemoglobin, the methemoglobin concentration decreased initially and then remained unchanged, whereas the aminophenol concentration remained high. Repeated additions of the *p*-Methylaminophenol Sulfate to the same erythrocyte solution had no greater effect on the methemoglobin concentration.

In a second part of the same study, *p*-Methylaminophenol Sulfate was injected intravenously into dogs and cats. The *p*-Methylaminophenol Sulfate was administered at a dose of 15 mg/kg, and after 2 min, the concentration in the blood was 3 μg/ml. The methemoglobin reached its maximum concentration (approximately 7 g/100 ml blood) in both species in 5 to 10 min. In cats, the effect of the dose of *p*-Methylaminophenol Sulfate "increased in proportion to the logarithm of the dose over a wide range of doses." The slopes of the lines characterizing the increase of effect of a particular

TABLE 1. PRODUCT FORMULATION DATA FOR *p*-METHYLAMINOPHENOLSULFATE[23]

Product Category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*		
			>5–10	*>0.1–1*	*≤0.1*
Hair dyes and colors	1073	49	1	17	31
1989 Totals		49	1	17	31

aminophenol with the log dose were similar for all of the aminophenols tested, but it was noted that the activities of the individual aminophenols varied independently of these slopes.

The authors concluded that the differences between species with regard to the rates of reaction of the aminophenols with hemoglobin were due to the differences in structure of the various hemoglobins. Because both *p*-Methylaminophenol Sulfate (and similar *p*-alkylaminophenols) and *o*-aminophenol cause a rapid increase in methemoglobin concentration and because there is a dose–response relationship, the authors suggested that these aminophenols may be useful for rapid alleviation of the effects of cyanide poisoning.[28]

Absorption, Distribution, Metabolism, and Excretion

p-Methylaminophenol Sulfate is structurally similar to other aminophenols, and the data available on these[11–14] may be useful for assessment of the absorption, distribution, metabolism, and excretion of *p*-Methylaminophenol Sulfate. In addition, because of the similar chemical behavior of the hair dye intermediates previously mentioned, an understanding of the data presented in the completed hair dye reports may provide a better understanding of the potential pathway of *p*-Methylaminophenol Sulfate in the body. Because *p*-Methylaminophenol Sulfate is a substituted aminophenol, the summary of the metabolism data from the Cosmetic Ingredient Review safety assessment of the aminophenols, specifically *p*-aminophenol (PAP), is presented here.[14]

> *In vivo* and *in vitro* studies of skin absorption have been performed using radioactive PAP, MAP [m-aminophenol], phenols and other hair dye intermediates. As much as 11 percent of the radioactivity introduced as ^{14}C-PAP in a simple vehicle was detected in the excreta, viscera and skin of rats after topical application. Hepatic metabolism of aminophenols includes such reactions as glucuronidation, sulfation and acetylation to form aminophenol-conjugates excreted in the urine.[14]

Because the amino group of *p*-Methylaminophenol Sulfate is methylated, this ingredient would not be expected to be acetylated.

In addition, data in the aminophenols report indicated that PAP was not metabolized by tissue preparations of pulmonary and renal microsomes from the rabbit, rat, and mouse.[14]

ANIMAL TOXICOLOGY

Acute Toxicity

Intravenous

In a study to determine the varying effects of aminophenols on hemoglobin and oxygen *in vitro* and *in vivo*, the i.v. LD_{50} for *p*-Methylaminophenol Sulfate in NMRI mice was estimated as 85 mg/kg.[28]

Groups of 5 female hooded rats were used in a comparative study of the nephrotoxicity of aspirin and its derivatives and of phenacetin derivatives (which are structurally similar to *p*-Methylaminophenol).[29] *p*-Methylaminophenol Sulfate was

administered intravenously to two groups of rats at doses of 0.1 mM/kg and 0.6 mM/kg. Renal proximal tubular necrosis was observed and was graded 1 to 4 to indicate the degree of severity. Necrosis of individual cells or groups of cells but not of all of the cells in adjoining tubules was defined as grade 1, and grade 4 was defined as necrosis of the entire proximal convoluted tubule. Those rats with grade 4 renal damage died in anuria, but the other test rats remained in good condition throughout the study. Those rats receiving the lower dose of *p*-Methylaminophenol Sulfate had grade 3 lesions of the tubules (necrosis of the distal third of all tubules as indicated by a band of necrosis in the inner cortex), whereas those rats receiving the higher dose had grade 4 lesions. The phenacetin derivatives were more nephrotoxic than aspirin and its derivatives, and the renal damage induced by the phenacetin derivatives was more clearly dose dependent than that caused by the aspirin derivatives. The authors concluded that a *para* arrangement of the amino and hydroxyl groups on the benzene ring was the basis for the nephrotoxicity of the phenacetin derivatives. In addition, substitutions on the amino group could also affect the nephrotoxicity of a particular compound, as in the case of *p*-Methylaminophenol Sulfate. The dose of *p*-aminophenol required to cause renal toxicity of grade 3 was approximately 20 times greater than that of *p*-Methylaminophenol Sulfate (2.1 mM/kg and 0.1 mM/kg, respectively).

Subchronic Dermal Toxicity

Two hair dye formulations containing 0.05% and 1.0% *p*-Methylaminophenol Sulfate were tested for dermal toxicity in groups of 12 adult New Zealand white rabbits.[30] These dye formulations contained other active ingredients in an aqueous solution and were mixed with an equal volume of 6% H_2O_2 prior to application. The formulations were applied twice weekly for 13 weeks to the clipped skin, with the skin of 3 rabbits of each group having been abraded at the beginning of each week. No significant differences were found between control and test animals with respect to body weight gain and urinalyses, and no discoloration of the urine was produced by the dyes. Statistically significant differences were found in some organ weights and in certain clinical chemistry and hematological values, but these were not considered toxicologically significant.

Chronic Dermal Toxicity

Two hair dye formulations containing 0.05% and 1.0% *p*-Methylaminophenol Sulfate were administered topically to groups of male and female Eppley Swiss Colony mice weekly for periods of 23 and 21 months, respectively.[31] The dye formulations were mixed with an equal volume of 6% H_2O_2, and a dose of 0.05 ml was applied to the clipped skin within 15 min. At the conclusion of the study, the survival rates and organ/body weight ratios of the test animals did not differ significantly from those of the controls, although there was considerable variation among the individual values.

Ocular Irritation

A 2% solution of *p*-Methylaminophenol in distilled water, 0.10 ml, was instilled into the conjunctival sac of the right eye of 6 albino rabbits, the eyes were not rinsed, and the untreated left eye served as a control.[32] The eyes were examined 1, 2, 3, 4, and

7 days after instillation of the test substance. The eyes were also examined under UV light with fluorescein dye. Three of the rabbits had no reaction to the *p*-Methylaminophenol. Of the remaining 3 rabbits, 1 rabbit had slight redness of the conjunctiva on days 1 and 2, clearing by day 3; 1 rabbit had slight redness of the conjunctiva on day 1 that had cleared by day 2; and the third rabbit had severe redness of the conjunctiva that moderated through days 2 and 3 and cleared by day 4. This rabbit also had a slight discharge on day 1 that did not continue through day 2. The test group average irritation score on day 1 was 2 out of a total possible score of 110; on day 2, the group average was 1/110; on day 3, the group average was 0.33/110. The score was 0 for the rest of the study. *p*-Methylaminophenol was considered practically nonirritating to the rabbit eye.

Dermal Irritation and Sensitization

Dermal Irritation

The primary irritation potential of *p*-Methylaminophenol was assessed using 6 albino Bouscat rabbits, equally divided by sex.[33] *p*-Methylaminophenol, 0.5 ml of a 2% solution in distilled water, was applied under a patch to abraded and intact skin on the flanks of each rabbit. The patches remained in place for 24 h. The test sites were evaluated 1/2 h after patch removal and again 48 h later. Two rabbits had slight erythema at both the intact and the abraded sites at both readings. One rabbit had slight erythema at both sites at the first reading, and 1 rabbit had slight erythema at the abraded site at the first reading. These reactions had subsided by the 48 h reading. The remaining 2 rabbits had no reactions. The primary irritation index (PII) for *p*-Methylaminophenol was 0.74 out of a maximum of 8, and the ingredient was considered slightly irritating to rabbit skin.

Dermal Sensitization

The skin sensitization potential of *p*-Methylaminophenol was evaluated using 20 albino Hartley guinea pigs, 10 of each sex.[34] A preliminary study to determine the dose of *p*-Methylaminophenol to be used in the challenge phase of the definitive study had been previously done using 4 Hartley guinea pigs and doses of 0.25 g and 0.5 g of undiluted *p*-Methylaminophenol per animal. Patch sites were evaluated 1, 6, 24, and 48 h after patch removal. Because the test substance caused a slight discoloration of the skin, erythema scores made at 1 h were not accurate. None of the guinea pigs had any sign of erythema or edema at any of the scorings. No evidence of sensitization was noted during the study. The dose of *p*-Methylaminophenol to be used during the challenge phase of the definitive sensitization study was determined to be 0.5 g. At the start of the definitive study, 6 h after the area behind the left shoulder blade of each guinea pig had been shaved, 0.5 g of *p*-Methylaminophenol was applied under an occlusive patch to the shaved area, where it remained for 48 h. Evaluations of the site were made 1, 6, 24, and 48 h after patch removal. Any of the animals that had signs of orthoergic reactions were eliminated from the study. During the induction phase of the study, 0.5 g of *p*-Methylaminophenol was applied under an occlusive patch to the shaved area behind the right shoulder blade every Monday, Wednesday, and Friday for 3 weeks and on the Monday of week 4. Patches remained in place for 48 h. Twice during the induction phase, at the first and fifth patch applications, the test site was injected with 0.1 ml of Freund's complete adjuvant at a concentration of 50% in sterile

isotonic saline. After removal of the final (tenth) patch, there was a 12-day nontreatment period. At the end of this period (day 36 of the study), an area on the left flank of each guinea pig was shaved, and 0.5 g of the test substance was applied under an occlusive patch, remaining in place for 48 h. Evaluations of the challenge site were made 1, 6, 24, and 48 h after patch removal, and erythema and edema were scored on a scale of 1 to 4. Histological examinations were performed on any animal that had lesions or in which a doubtful reaction was noted. Two of the guinea pigs died during the study; death was not related to treatment with *p*-Methylaminophenol. Of the 18 remaining guinea pigs, 3 had doubtful signs of erythema, 2 at the 6 h evaluation, and 1 at the 24 h evaluation. No reactions were noted in the other 15 guinea pigs. Biopsies were performed on the 3 animals that had doubtful reactions. The stratum corneum, cuticle, dermis, and appendages were examined, and no signs of sensitization were noted. *p*-Methylaminophenol was not considered a dermal sensitizer under the conditions of the study.

Teratogenicity

Two hair dye formulations containing *p*-Methylaminophenol Sulfate at concentrations of 0.05% and 1% were tested by topical application at a dose of 2 ml/kg every 3 days for a total of seven doses during gestation to the shaved dorsoscapular region of groups of 20 mated Charles River CD female rats.[30] The hair dye ingredients were in aqueous solution, and there were other active ingredients, such as phenylenediamines and aminophenols, present in the solutions. The hair dyes also were mixed with 6% H_2O_2 before application. No significant embryotoxic or teratogenic effects were observed.

MUTAGENICITY AND CARCINOGENICITY

Mutagenicity

p-Methylaminophenol was tested for mutagenic potential in the Ames assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538.[35] The positive control was 2-aminoanthracene. *p*-Methylaminophenol was tested at concentrations ranging from 30 μg to 2.0 mg. Though *p*-Methylaminophenol did not appear to be mutagenic, it was toxic to the bacterial cells, especially to strains TA98 and TA1538, in the absence of S-9 mix. *p*-Methylaminophenol, at concentrations ranging from 8 to 500 μg/plate, was retested in strains TA98 and TA1538 with metabolic activation to determine whether possible mutagenic activity was masked by the toxicity of the compound when not detoxified by the S-9 mix. No mutagenic activity was noted in the repeat test, and *p*-Methylaminophenol was considered nonmutagenic in the Ames assay.

The micronucleus test also was used to determine the mutagenic potential of *p*-Methylaminophenol.[36] Groups of 10 male Swiss mice were administered two i.p. injections 24 h apart of 50, 75, or 100 mg/kg *p*-Methylaminophenol. A vehicle control (Baker water) group also was included. The mice were killed, and bone marrow was extracted from the femurs of each mouse 30 h after the first injection. Two smears were made from each mouse. When the smears were dry, they were colored with May Grundwald Giemsa. The number of micronuclei-containing polychromatophile eryth-

rocytes were recorded out of a sample of 2000 polychromatophile erythrocytes per mouse. An increase in the number of micronuclei was considered evidence of mutagenic action. Under the conditions of the study, *p*-Methylaminophenol was considered nonmutagenic in the mouse micronucleus assay.

p-Methylaminophenol was tested for mutagenic potential in the chromosome aberration test using Chinese hamster ovary (CHO) cells.[37] CHO cells were treated for 1 h, with and without metabolic activation, with 0.125, 0.25, 0.5, or 1 mg/ml *p*-Methylaminophenol. Usually, the cells that are exposed to the test chemical without metabolic activation remain in contact with the test chemical until fixation at 6, 12, or 16 h, but because of the toxicity of the *p*-Methylaminophenol, treatments were administered for 1 h only for assays with or without metabolic activation, and fixation times remained at 6, 12, and 16 h. Methyl methanesulfonate (MMS) and cyclophosphamide were the positive controls. Chromosomal aberrations were scored per 100 metaphasic cells. A positive response was indicated when the frequency of aberrations increased in a dose-dependent manner. The 1 mg/ml dose resulted in few, if any, metaphases, and only doses of 0.5 mg/ml and below were scored. Though *p*-Methylaminophenol was quite toxic to CHO cells, no evidence of mutagenic potential was observed under the conditions of the study.

Carcinogenicity

In the chronic dermal toxicity study previously described,[31] the mice also were evaluated for neoplasms at the end of the 21 and 23-month treatment periods. Of special interest were neoplasms of the skin, which were of low incidence. Several other types of neoplasms were found at necropsy and microscopic evaluation, but none of the incidences were statistically significant. The authors concluded that the hair dye formulations tested did not have any carcinogenic effects.

CLINICAL ASSESSMENT OF SAFETY

Occupational Studies

Because certain chemicals used in photographic developing were known to cause skin diseases, an evaluation of the skin diseases reported by employees at a film developing plant was undertaken.[22] The study was an attempt to determine the frequency and types of occupational and nonoccupational dermatoses among the plant employees. The study consisted of five parts. In the first part, the employees responded to a questionnaire detailing their previous and current tasks at the plant and any previous or current skin diseases. In the second part of the study, all of the questionnaire respondents who had indicated previous or current skin diseases were invited to be examined by a doctor. At the examination, the patients were questioned about any skin problems (past or present) and about their tasks at the plant. If any skin lesions were present, these were examined, noted, and treated. A preliminary assessment of any correlation between skin disease and job was made at this time. In the third stage of the study, those patients who were thought to have occupationally related dermatoses were offered the chance to be patch tested with 11 standard series substances and with 20 film laboratory chemicals. The patches remained in place for 48 h and were scored 24 h and 2 to 3 weeks after patch removal. At this stage in the study, 23 patients were tested

with Metol (*p*-Methylaminophenol Sulfate). Of the 23 test subjects, 6 had positive reactions to Metol at concentrations of 5% and 1%. Of these 6 subjects, 3 were also positive for either two or three of the following chemicals: CD-2, CD-3 (chemical name not specified), *p*-phenylenediamine (PPDA), and PBA-1 (persulfate bleach accelerator-1, found to be a potent sensitizer). Metol, at a concentration of 1%, was then tested on a group of 200 control subjects (eczema patients without known previous contact with the chemical), and 1 subject had a positive reaction. The fourth and fifth stages of the study involved testing five different glove materials for protection against Metol and chemical CD-2 and a guinea pig allergy test on another chemical, PBA-1. Forty-nine percent of the film laboratory employees had been afflicted with occupational dermatoses directly related to their work with film laboratory chemicals. Contact allergies to the chemicals Metol, CD-2, CD-3, and PBA-1 were found in 28% of the employees working with the chemicals. In many of these contact allergy cases, the reactions had been so severe that the employees had either seen a doctor, changed jobs, or taken sick leave.

EPIDEMIOLOGY

There have been a number of studies published attempting to determine a possible correlation between the use of hair dyes and an increased risk of cancer.[11] Clemmesen[38] has reviewed many of these reports, pointing out the difficulties involved in epidemiological studies, such as small sample sizes, varying intensities and durations of exposure, lag times, and lack of consideration of such lifestyle factors as tobacco consumption. Because of these deficiencies, he concluded that there was not a positive correlation between hair dye use and an increased risk of cancer. His conclusion was supported by a later study of 401 breast cancer patients and 625 age-matched controls without breast cancer in whom no significant differences were found between the two populations with regard to the frequency, duration, type, shade, and application times of hair dyes.[39]

SUMMARY

p-Methylaminophenol Sulfate is a substituted phenol used as a dye and a photographic developer. It is manufactured by the methylation of *p*-aminophenol followed by neutralization with sulfuric acid. *p*-Methylaminophenol Sulfate may be determined analytically by infrared, ultraviolet, and nuclear magnetic resonance spectra, by thin layer chromatography, and by visual or potentiometric titration. *p*-Methylaminophenol Sulfate absorbed in the UV range at 220 and 271 nm, whereas *p*-Methylaminophenol absorbed at 219, 270, and 277 nm.

In oxidative hair dyes, *p*-Methylaminophenol Sulfate is used as a primary intermediate. It reacts with an oxidant to produce the corresponding imine, which then reacts with a coupler to form an indophenol dye. It is listed as an ingredient in 38 hair dye formulations, its concentration ranging from $\leq$0.1% to 0.1–1%. In addition, it is listed at concentrations of $>$ 1–5% and $>$5–10%, respectively, in two powder dye formulations that are to be diluted before use.

p-Methylaminophenol Sulfate was an inhibitor of the depolarizing action of acetylcholine on the giant neurons of *Lymnea stagnalis*. In the erythrocytes of oxen, dogs, rabbits, and humans, *p*-Methylaminophenol Sulfate caused the formation of methemoglobin at a much greater rate than did *p*-aminophenol.

In skin absorption studies of radioactive *p*-aminophenol, as much as 11% of the radioactivity was found in the excreta, viscera, and skin of rats. Aminophenols undergo glucuronidation, sulfation, and acetylation reactions in the liver. The aminophenol conjugates formed in these reactions are excreted in the urine. *p*-Aminophenol was not metabolized by tissue preparations of pulmonary and renal microsomes from several species.

The intravenous LD_{50} of *p*-Methylaminophenol Sulfate in NMRI mice was 85 mg/kg. The dose of *p*-Methylaminophenol Sulfate causing necrosis of the distal third of all tubules of the kidneys of hooded rats was 0.1 mM/kg, 20 times greater than the dose of *p*-aminophenol required to produce the same effect.

In subchronic and chronic dermal toxicity studies of hair dyes containing *p*-Methylaminophenol Sulfate, among other active ingredients, no toxicologically significant differences were observed between the test and control animals (rabbits and mice, respectively).

In an ocular irritation study, *p*-Methylaminophenol was considered practically nonirritating to the rabbit eye.

p-Methylaminophenol was slightly irritating to rabbit skin in a primary irritation study and was not considered a dermal sensitizer in a guinea pig skin sensitization study.

No significant embryotoxic or teratogenic effects were found when hair dyes containing *p*-Methylaminophenol Sulfate and other active ingredients were administered topically to Charles River CD rats once every 3 days for a total of 21 days during gestation.

p-Methylaminophenol was not mutagenic in the Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. The *p*-Methylaminophenol was toxic to the bacterial cells, especially to those of strains TA98 and TA1538, in the absence of metabolic activation. Additional testing in strains TA98 and TA1538 with metabolic activation indicated that the toxic effect of the *p*-Methylaminophenol did not mask any possible mutagenic effect. *p*-Methylaminophenol was nonmutagenic in the mouse micronucleus assay and in the Chinese hamster ovary chromosome aberration test.

No statistically significant incidences of neoplasms, dermal and other, were found in mice after 21 and 23 months of weekly dermal exposure to hair dyes containing *p*-Methylaminophenol Sulfate in addition to other active ingredients.

Of 23 panelists known to have occupationally related dermatoses who were patch tested with *p*-Methylaminophenol Sulfate, 6 had positive reactions to the ingredient at concentrations of 1 and 5%. Three of these panelists also had positive reactions to two or three of a group of four chemicals used in film laboratories. When *p*-Methylaminophenol Sulfate was tested in 200 eczema patients without known previous contact with the chemical, 1 patient had a positive reaction.

A number of studies have been performed in order to determine the possibility of a correlation between the use of hair dyes and an increased risk for cancer. No positive correlation has been found.

CONCLUSION

On the basis of the available data presented in this report, the CIR Expert Panel concludes that *p*-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

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